Specialty Conference

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Cerebellar Ataxia

Anatomical, Physiological and Clinical Implications

PIERRE M. DREYFUS, MD:* *Ataxia, or the inability to coordinate voluntary movements, constitutes a dramatic and important neurological symptom that is usually indicative of structural disease of the nervous system. Ataxia can result from lesions in a variety of different anatomical sites: peripheral nerves, spinal cord, brain stem, cerebellum, and frontal or parietal lobes. Ataxia also occurs in diseases affecting the labyrinth of inner ear and it may be caused by drugs and toxic substances. Finally, ataxia may be of psychiatric origin—hysteria or malingering.*

The diagnosis of ataxia is best determined by clinical maneuvers that show either the inability to dissociate movements requiring skill and speed (dyssynergia) or to gauge speed, distance or power of a movement (dysmetria), or a disturbance of the function of reciprocally innervated muscle groups with diametrically opposed function (dysdiadochokinesia). In addition, alterations in tone (hypotonia) and reflex activity (hyporeflexia) or pendular reflex activity, and abnormal movements, such as intention, action or resting tremor, can sometimes be shown.

In this specialty conference, the topic of ataxia caused by dysfunction of the cerebellum or its connections will be discussed. An attempt will be made to review briefly some basic aspects of cerebellar anatomy and physiology and to discuss some of the common neurological disorders of adults and children in which cerebellar ataxia is a prominent feature. These diseases are, for the most part, not treatable. However, a few are amenable to treatment that results in definite improvement, and some are completely reversible.

Dr. Oshtory will now present the case of a patient whose chief complaint was that of progressive ataxia.

Case Presentation

MEHERJI OSHTORY, MD:‡ A 45-year-old alcoholic white man presented to the Sacramento Medical Center because of progressive unsteadiness of gait.

One year before admission, the patient began having difficulty with balance. He stumbled and fell frequently when confronted with obstacles in his path and he often reached for support to maintain balance. His neurological deficit progressed steadily to the point that he walked with his feet far apart, held onto objects and had great difficulty in turning. The patient became aware of an increased tendency to sway and had fallen frequently during the months before admission to hospital.

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He said that weakness, loss of consciousness, headache, visual disturbance, vertigo, tinnitus, weight loss and anorexia had not been problems.

Neither the patient's medical history nor his family medical history included any relevant material. The patient lived in a boarding home and his drinking habits varied according to his financial status. His average alcohol consumption had varied from a fifth (one fifth of a gallon) to a quart of alcohol (whiskey or gin) per day for some years. His nutritional intake was marginal, depending largely on his appetite, alcohol consumption and financial reserves.

When admitted to hospital the patient was seen to be undernourished and had a small bruise on the left forehead, incurred during a recent fall. Vital signs were normal. Examination of the chest, heart, abdomen, genitalia and rectum showed no abnormalities.

On neurological examination the patient was cooperative and oriented in all spheres. The cranial nerves were normal except for mild horizontal and vertical nystagmus, most pronounced on left lateral gaze.

The patient was unable to stand upright and still with his feet together; he assumed a broadened base and there was a moderate degree of truncal ataxia. His gait was extremely ataxic and he had to hold onto furniture or walls near him for support. Executing turns was particularly difficult for him because he tended to fall in the direction of the turn. Power and tone were normal in all extremities and no involuntary movements could be elicited.

Tests for coordination showed a mild intention tremor in both upper extremities. Rapid alternating movements were done normally. The heel to shin test showed moderate impairment bilaterally and dysmetria of rapid foot tapping was noted.

Deep tendon reflexes were normal and symmetrical in the upper extremities. In the lower extremities, knee jerks were present bilaterally and equal, but the right ankle jerk was absent and the left ankle jerk was notably diminished. Abdominal and cremasteric reflexes were intact bilaterally. Plantar responses were flexor.

On sensory examination there was mild impairment of vibratory sense over both ankles and toes; other modalities were intact.

Laboratory examinations showed a hematocrit of 38.9 percent and hemoglobin value of 13.3 grams per dl. Mean corpuscular volume was 107 and the blood smear showed macrocytosis and variation in size and shape of red cells. Total leukocyte count, sedimentation rate, electrolytes and levels of serum protein, hepatic enzymes, serum vitamin B_{12} and folic acid were all within normal limits. X-ray studies of the chest and the skull showed no abnormalities. EEG, brain scan, and spinal fluid examinations were normal.

Comments

Because of the insidious onset of truncal ataxia in the absence of demonstrable systemic disease,

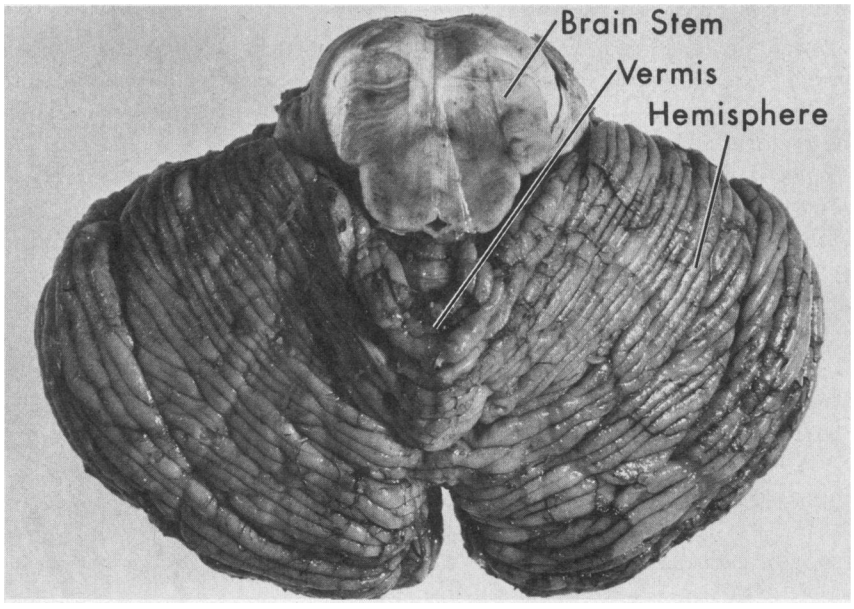

Figure 1. — Superior view of the cerebellar hemispheres. (Courtesy of Drs. G. York and W. Ellis.)

the diagnosis of cerebellar degeneration associated with chronic alcoholism was entertained.

DR. DREYFUS: *Thank you, Dr. Oshtory. I have asked Dr. Gardner to discuss briefly the applied anatomy of cerebellar ataxia.*

Applied Anatomy of Cerebellar Ataxia

ERNEST D. GARDNER, MD:* The human cerebellum lies in the posterior fossa, in an infratentorial position. It is connected to the brain stem by three pairs of peduncles and is grossly divisible into two hemispheres and a median portion termed the vermis (Figures 1-3). The cerebellum receives its arterial supply from the vertebral-basilar system. It is important to emphasize the infratentorial position of the cerebellum, and its relationships to the tentorial notch above, the foramen magnum below, and the fourth ventricle and brain stem in front. Expanding lesions of the cerebellum may result in herniation upward or downward, and may compromise the ventricle, the circulation of cerebrospinal fluid, and the brain stem and its cranial nerves.[1]

The hemispheres and vermis of the cerebellum are deeply partitioned into folia and lobules that have a complex terminology (often based upon comparative neuroanatomy) that need not concern us here. What should be emphasized is that

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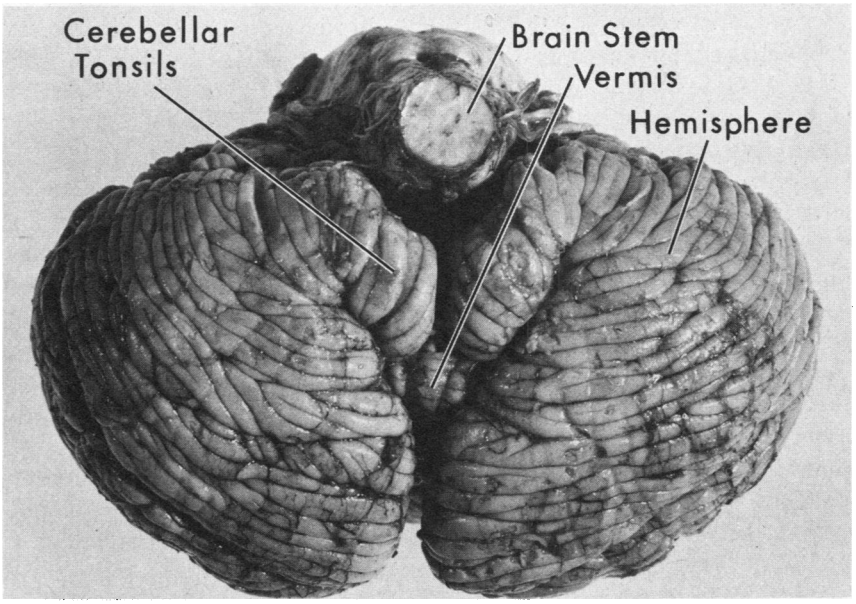

Figure 2.—Inferior view of the cerebellar hemispheres. (Courtesy of Drs. G. York and W. Ellis.)

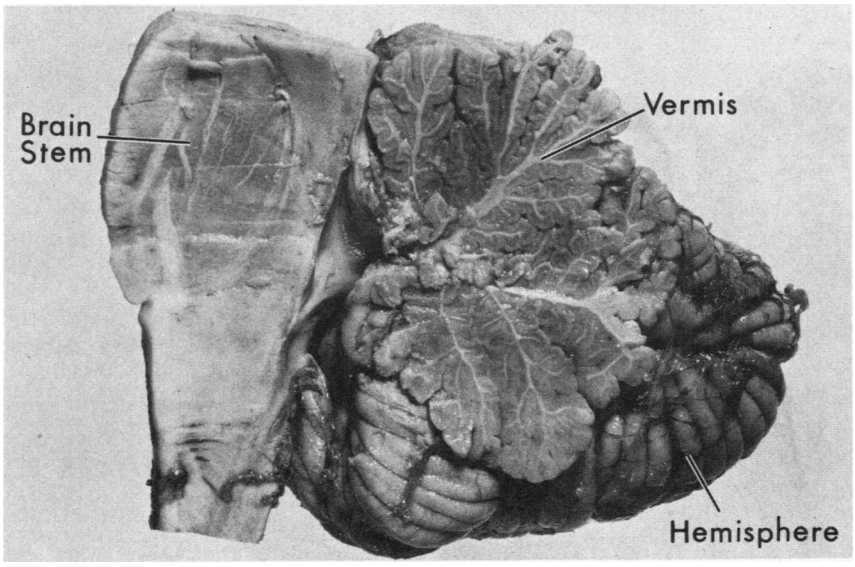

Figure 3.—Sagittal view of the cerebellar hemispheres showing the vermis. (Courtesy of Drs. G. York and W. Ellis.)

the cerebellum—in common with the cerebrum—has a surface layer of gray matter, but that—in contrast to the cerebrum—its cortex is of uniform thickness and synaptic arrangement.[2] Leaving aside the details of cortical structure, it can be stated that the cortical output is by way of the axons of Purkinje cells. These axons for the most part project to the intracerebellar (deep) nuclei, which are masses of gray matter contained within the white matter that forms the interior of the cerebellum. Axons from nerve cells in these nuclei, in turn, leave the cerebellum and comprise the cerebellar output.

In order to carry out its functions, the cerebellum requires information about the position of the body, angles and torsion at joints, tension in muscles and tendons, frequency of muscular contraction, states of autonomic functions, stimulation of skin and subcutaneous tissues and special sense organs, and activity in cerebral cortex and basal ganglia.[3] Signs of cerebellar dysfunction, including ataxia, may arise if information does not reach the cerebellum, if the cerebellum itself is involved or if the cerebellar output is interrupted. In addition, some circuits of the cerebellum appear to be preset—that is, genetically determined—and when activated (perhaps by signals from the cerebral cortex) may bring about a pattern of movement before receiving any information from peripheral receptors.

It is a matter of clinical importance that the control mediated by the cerebellum is largely ipsilateral—for example, the right cerebellar hemisphere is related to the right half of the body. It may be that this relationship is even more precise, that a specific area of a cerebellar subdivision may have input-output connections with a specific part of the body, such as a limb. However, concrete evidence for this specificity in humans is still lacking.

Cerebellar Input and Output

Nerve impulses that comprise the cerebellar input reach the cerebellar cortex by way of pathways that enter the cerebellum over its peduncles. Whatever the pathway, the constituent fibers are usually well myelinated and rapidly conducting. The impulses that comprise the output leave, for the most part, from the deep cerebellar nuclei by way of or adjacent to the peduncles. The input-output arrangements can also be termed loops, the general principles of which are briefly outlined below (Figure 4).

Vestibular Loop

Impulses initiated by the stimulation of receptors in the vestibule and semicircular canals—that is, by the position of the head and by linear and rotational movements of the head—reach a small portion of the inferior cerebellum termed the flocculonodular lobe (also called the archicerebellum). The output is to those vestibular, reticular and motor nuclei of the brain stem that are concerned with the control movements of the eyes, head, neck and upper trunk.[1]

Disorders of this loop resemble vestibular disorders. Moreover, this part of the cerebellum is the common site of origin of medulloblastomas.

Spinal Loop

Impulses initiated by the stimulation of receptors in skin, muscles, tendons and joints (especially of the limbs) reach the cerebellum first by a number of ascending spinal pathways (and certain brain stem pathways) and then by way of the inferior and superior cerebellar peduncles. The portion of the cerebellum to which these impulses are chiefly directed is the vermis, sometimes termed the paleocerebellum. The output is from certain of the deep cerebellar nuclei by way of the inferior peduncle and is directed to those vestibular and reticular nuclei of the brain stem that are especially concerned with the control of limb musculature.[1]

It is important to emphasize that the multiplicity of spinal pathways provides a wide margin of safety. Consequently, ataxia from spinal lesions can be temporary unless there is widespread specific involvement of these paths.

Neocortical Loop

The cerebellar hemispheres (sometimes termed the neocerebellum), which are as prominent in humans as are the cerebral hemispheres and cortex, receives a massive input from the neocortex of each cerebral hemisphere. The impulses are carried by fibers that descend in the internal capsules and cerebral peduncles to the pons, where they are relayed to the cerebellum by axons that form the middle cerebellar peduncles.[1]

The output of the neocerebellum is chiefly from the dentate nuclei (or the deep nuclei), whose axons form most of the superior cerebellar peduncles. The axons of a given superior peduncle cross in the midbrain, where some end in the red nucleus. Others continue to the thalamus (to the same nuclear region that relays impulses

from certain basal ganglia) and thence back to the cerebral cortex, especially the motor cortex. The projection to the thalamus is sometimes known as the dentato(rubro)thalamic path.[1]

It is evident that the neocerebellum, which comprises the bulk of the cerebellum, forms two extensive contralateral loops with the cerebral cortex, including the thalamus, and that it also has significant descending connections.[4] Signs of cerebellar dysfunction, including ataxia, can result from involvement not only of the cerebellar hemispheres but also of the input-output portions of the loops. However, as in the case of the spinal loop, the multiplicity of connections and their widespread nature often provide a wide margin of safety.

Other Relationships

It is of some interest to note that the cerebellum receives a significant input from the visual and auditory systems by way of tectocerebellar fibers. Also the cerebellum has significant connections with the autonomic centers of the brain stem. The precise nature and functions of these additional relationships are still uncertain.

This brief outline of cerebellar anatomy is intended to serve as a basis for the physiological and clinical discussions that follow.

DR. DREYFUS: *Thank you, Dr. Gardner, for a most lucid discussion. Dr. Lieberman will now review briefly the practical aspects of cerebellar physiology.*

Practical Aspects of Cerebellar Physiology

JAMES S. LIEBERMAN, MD:* Recent studies concerning cerebellar physiology have been focused upon either the basic information-processing properties of the organ or the relationship of cerebellar function to clinical dysfunction.[4-6,9]

It is now quite clear that the cerebellum is a very complex neural organ that functions basically as an error-detecting and error-correcting computer concerned with the smooth control of movement.[4,5] In addition it plays an important role in the maintenance of muscle tone and, in fact, may also play a role in the initiation of certain movements.

As detailed in the section on applied neuroanatomy, the cerebellum consists of a cortex and

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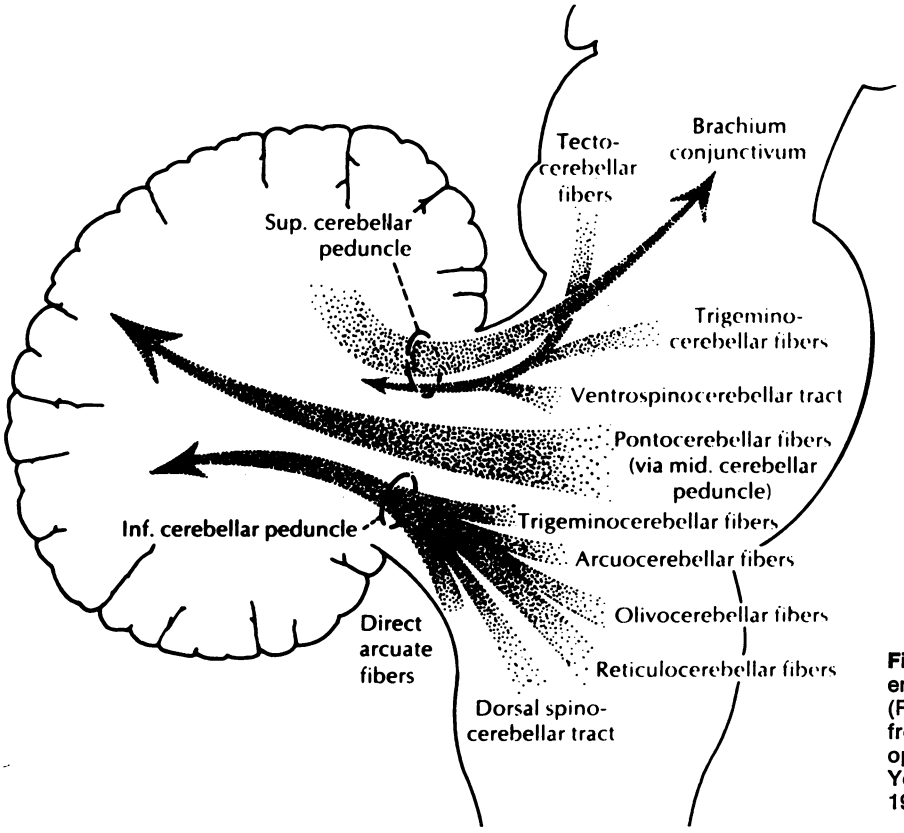

Figure 4.—Afferent and efferent cerebellar connections. (Reproduced with permission from Matzke and Foltz: Synopsis of Neuroanatomy. New York, Oxford University Press, 1967.)

a system of deep cerebellar nuclei. All of the neurons of both the cerebellar cortex and nuclei are in a state of continuous activity, with a resting firing rate of 20 to 100 Hz as they await synaptic input signifying the arrival of information from afferent pathways. Therefore, each cell is already "primed" to respond to synaptic input by raising or lowering its firing frequency.[4,5]

Afferent information to the cerebellum is delivered to the cerebellar cortex by either the climbing fiber system via the olivary nuclei or from all other afferent paths via the mossy fiber system. Experiments show that stimulation of mossy fibers excites granule cells and their axons, the parallel fibers; this in turn leads to excitation of Golgi cells, basket cells, superficial stellate cells and, finally, Purkinje cells. Within the subcircuitry both excitatory and inhibitory pathways exist, but the net effect of the system is felt to be inhibition of cerebellar nuclear cell discharge. The climbing fiber pathway, having arisen from inferior olivary cells, provides monosynaptic excitatory connections with Purkinje cells, and also provides connections with Golgi cells and interneurons via a system of collaterals. Again, the net result of climbing fiber stimulation is inhibition of cerebellar nuclear cell discharge. It is now known that all input to the cerebellar cortex by whatever pathway becomes inhibitory within at most two synaptic relays. Therefore, the entire output of the cerebellar cortex is via Purkinje cell discharges that provide an inhibitory sculpturing of nuclear cell discharges.[4,5]

The cerebellar efferent system consists of projections from the cortical Purkinje cells to the lateral vestibular nuclei, and to the deep cerebellar nuclei. In contrast to the inhibitory effects of cerebellar cortical output, cerebellar nuclear output is basically excitatory with respect to motor function. For example, it has now been concluded that the neocerebellum mediates a tonic facilitatory effect on the dentato-rubro-thalamo-cortical pathway.[6-9] As a result, it can be concluded that, except for direct vestibular connections, the net output of the cerebellum is facilitatory via the nuclear system, as modified by an inhibitory cerebellar cortical system.

Studies primarily concerned with basic information-processing properties of the cerebellum have not always been directed toward an explanation of clinical cerebellar dysfunction. However, several recent studies have provided much information with regard to the pathophysiology of cerebellar signs. These signs in experimental animals were described in the late 19th century, and the Croonian Lectures by Holmes in 1922[10] are regarded as the definitive description of cerebellar disease in man. It is interesting to note that Holmes felt that hypotonia was the most consistent abnormality present and that other important clinical signs, such as dysmetria or tremor, could be due to hypotonia.

Showing the function of the gamma efferent-muscle spindle afferent system and the relationship of the cerebellum to this system has provided the basis for much of the recent research into the physiological basis of cerebellar hypotonia. It has now been clearly shown that (1) a depression of fusimotor efferent and spindle afferent activity results from cerebellar ablation, (2) this depression can be correlated with clinically observable decreased muscle tone (hypotonia) and (3) in an animal with a chronic cerebellar ablation, fusimotor efferent or spindle afferent activity (or both) recovers as hypotonia disappears.[6]

The pathways by which the cerebellum facilitates fusimotor activity have been studied in detail. The anatomic pathways are now well described. Present information suggests that both the fastigio-bulbar pathway and the dentato-rubro-thalamic pathway are involved in the mechanisms of hypotonia. The contribution of each pathway varies from species to species. In lower mammals the fastigial pathway is probably more important while the dentato-rubro-thalamic (neocerebellar) pathway is more important in primates.

Many experiments have been designed to strengthen the theory that hypotonia is a result of diminished neocerebellar facilitation of fusimotor activity. Section of the superior cerebellar peduncles, lesions of the ventrolateral nucleus of the thalamus, ablations of motor cortex and section of the medullary pyramid have all been shown to lead to decreased muscle spindle responses.[6-9]

While the mechanism of cerebellar hypotonia is relatively well understood, the mechanism of other cerebellar signs, including tremor, is poorly worked out. Currently available information would seem to indicate that cerebellar tremor is related to the mechanism of movements projected into the environment, and that the thalamus and areas 4 and 6a of the cerebral cortex may be important in its genesis. Some recent experiments

have suggested the presence of tremor generators within the central nervous system. Both a thalamo-cortical system and an olivo-cerebellar system for generating tremor have been described.[11] It is felt by some investigators that a relative imbalance between the two systems might be the cause of either the intention tremor of cerebellar disease or the resting tremor of basal ganglia disease.

The cause of the ataxia or dysmetria seen in cerebellar disease has been the subject of much recent investigation. The analogy of the cerebellum as an error-detecting and error-correcting computer consisting of several servo loops has led to analysis of dysmetria by both physiologists and servo engineers. It is now becoming evident that lesions in cerebellar pathways (input pathways, output pathways or cerebellum proper) lead to interruption of feedback loops. This feedback loop interruption then results in excessive "oscillation" within the system, producing an instability in the final product—movement.[5] This instability of movement is observed clinically as dysmetria, dyssynergia, dysdiadochokinesia and, perhaps, tremor.

DR. DREYFUS: *Thank you, Dr. Lieberman. Next, I wish to discuss neurological diseases characterized by ataxia that have their onset in adulthood.*

Cerebellar Ataxia in the Adult

Classification of the cerebellar ataxias of adulthood tends to be extremely arbitrary. It seems most appropriate to divide these diseases into three categories: (1) acute, (2) subacute and (3) chronic (see Table 1).

The most common subacute form is the cerebellar ataxia associated with chronic alcoholism, although this disease may present in an acute form. The fact that persistent cerebellar dysfunction can result from chronic, abusive ingestion of alcohol was not generally accepted until 1959, when Victor and his colleagues presented a detailed account of cerebellar degeneration in 50 patients. The clinical and pathological manifestations of the disease are remarkably stereotyped. The syndrome is characterized by a wide-based stance and gait, varying degrees of instability of the trunk and ataxic movements of the limbs. The legs are invariably involved to a greater extent than are the arms, which may be completely spared. Hypotonia of the limbs, nystagmus and dysarthria are relatively infrequent findings.[12]

TABLE 1.—*Cerebellar Ataxia in Adults*

Acute
Intoxications
Alcohol, barbiturates, phenytoin and other anticonvulsants, heavy metals (lead and mercury)
Tumors
Primary, metastatic
Viral infection
Hyperpyrexia
Vascular accidents: hemorrhage and infarction
Demyelinating diseases
Subacute
Alcoholic cerebellar degeneration
Carcinomatous cerebellar degeneration
Chronic
Heredofamilial
Olivo-pontocerebellar atrophy
Parenchymatous cerebellar degeneration
Myxedema
Associated with multiple vascular lesions (von Hippel-Lindau)

In most cases the ataxic syndrome has an abrupt onset, manifesting itself rapidly over a period of several weeks; it then may remain unchanged for many years. However, in some instances, the syndrome evolves slowly over many months. Occasionally symptoms are aggravated by superimposed infection or a bout of delirium tremens.

The pathological changes are restricted to the anterior and superior aspects of the cerebellar vermis, where the major changes consist of degeneration of all of the neurocellular elements of the cerebellar cortex, the Purkinje cells being particularly affected. In advanced cases the anterior parts of the cerebellar hemisphere, the olivary and vestibular nuclei in the brain stem, and some of the so-called roof nuclei of the cerebellum are involved.[12]

In most instances the patient's condition stabilizes or improves upon cessation of drinking and institution of improved nutrition and vitamin supplementation.

Occasionally an acute ataxia in conjunction with Wernicke disease develops in patients. The cerebellar changes in these cases are indistinguishable from those seen in patients suffering from alcoholic cerebellar degeneration who do not have Wernicke disease.[13]

Although the cause of alcoholic cerebellar degeneration remains essentially unknown, there is good evidence that the syndrome is engendered by malnutrition. However, a toxic reaction of

Purkinje cells to metabolites of alcohol, such as acetaldehyde, has not been excluded as a causative factor.

Alcoholic cerebellar degeneration must be distinguished from the cerebellar degeneration caused by the remote effects of carcinomatosis.[12,14]

Remote Effects of Carcinoma

While it is well known that subacute cerebellar degeneration can be caused by the remote effects of carcinoma, the nature of the relationship between the two conditions remains obscure. A variety of neoplasms has been shown to be associated with cerebellar degeneration, the most common being carcinoma of the lung, breast, ovary and kidney. The syndrome may also occur in association with a variety of lymphomas.[14]

Although this disorder closely resembles the one engendered by alcohol, it is possible, on clinical grounds alone, to distinguish patients who have a cerebellar syndrome secondary to an occult neoplasm from those with chronic alcoholism. Victor,[14] summarizing the clinical and pathological data of 26 cases, found that in almost every instance of cerebellar degeneration associated with neoplasia the patient's arms were affected to an equal or greater extent than were the legs. Nystagmus and dysarthria were present in as many as 80 percent of the cases. In addition, in many of the patients there were symptoms and signs not ordinarily considered cerebellar in nature—such as diplopia, vertigo, spasticity, dysarthria, dementia, static and postural tremors, and sensory abnormalities. Spinal fluid abnormalities were noted in half of the cases, consisting of elevated protein in six cases, an abnormal colloidal gold solution curve in eight and an excessive number of lymphocytes in two.

Pathological examination showed more diffuse involvement of the cerebellum in cases of cerebellar syndrome secondary to an occult neoplasm than in patients with alcoholic cerebellar degeneration. All parts of the cerebellum seemed to be affected in the involved folia. All of the neurocellular elements showed pathological alterations and the net effect was Purkinje cell loss and thinning and narrowing of the granular and molecular layers.

It should be noted that in more than 50 percent of the cases of cerebellar degeneration associated with neoplasia the signs of cerebellar disease preceded the overt appearance of the underlying neoplasm by months and sometimes years.[14]

The pathogenesis of the disorder still is unknown. Malnutrition, alcoholism and a variety of toxins have been incriminated. The disease has been compared to the cerebellar degeneration observed in Kuru, which is known to be caused by a transmissible agent. It has been suggested that alterations in the overall immune response experienced by patients afflicted with neoplasia may be responsible either for the activation of a latent virus or for the invasion of a neurotropic virus.

Neoplasia can affect the cerebellum directly. Most primary tumors of the cerebellum, such as astrocytomas and medulloblastomas, tend to occur in childhood, while the neoplasms that most commonly affect the cerebellum of adults are tumors of the cerebellar pontine angle (acoustic neuroma) and metastatic tumors, predominantly from the lung.

Metastatic tumors of the cerebellum tend to present in either an abrupt or subacute manner. Unilateral and bilateral ataxia, signs of brain stem dysfunction, and early evidence of increased intracranial pressure are the most common clinical manifestations. Occasionally a metastasis in the midline of the cerebellum may present with truncal ataxia. This could be confused with either alcoholic cerebellar degeneration or the remote effects of carcinoma of the cerebellum. The use of computerized axial tomography helps in establishing the correct diagnosis.

Cerebello-pontine angle tumors, slow-growing tumors that emanate from cranial nerves in the vicinity of the cerebellum (8th, 7th, 5th), produce symptoms by compressing the cerebellum and its connections. Frequently these symptoms are preceded by tinnitus, progressive deafness and signs suggestive of involvement of cranial nerves. By the time cerebellar symptoms are clinically evident these tumors have reached a relatively large size. In view of the favorable response to surgical intervention, early diagnosis of these tumors is obviously important.

Disorders With Toxic Causes

A variety of organic compounds and heavy metals is known to affect the cerebellum. The most important of these are phenytoin (Dilantin®), 5-fluorouracil, the insecticide DDT, trichloroethylene, arsenic, mercury and manganese. The toxic effects of these compounds are not necessarily restricted to the cerebellum; other parts of the nervous system, including peripheral

nerves, may be involved. Phenytoin and other anticonvulsant medications are unique in that they seem to affect the cerebellum primarily. While the toxic effects of phenytoin tend to be transient, disappearing when the dose is reduced, irreversible cerebellar damage may ensue. The toxic effects of phenytoin are characterized by nystagmus to lateral gaze, which occurs when the blood drug levels rise above the therapeutic level of 20 mg per ml; with levels above 30 mg per ml, dysarthria and ataxia of gait and limbs appear.

Pathological studies in both experimental animals and humans have shown a pronounced loss of Purkinje cells with relative sparing of other cellular elements of the cerebellum following prolonged therapy with phenytoin.[15-17]

Cerebellar Hemorrhage

The diagnosis of cerebellar hemorrhage assumes great importance when we consider that early surgical evacuation of the hematoma is generally followed by good recovery. Unfortunately, diagnosis of this neurological entity is difficult to establish and is often missed. It has been suggested that the diagnosis of cerebellar hemorrhage should be seriously entertained in all patients under 30 years of age who present with the sudden onset of headache followed by evidence of brain stem dysfunction. It should also be considered in patients above the age of 45 suspected of having a subarachnoid hemorrhage. Cerebellar hemorrhage is usually signalled by the sudden onset of severe, occipital, generalized headache. Vomiting follows, then drowsiness, stupor and finally coma. The symptoms progress at varying rates, moving from one to another in a few minutes, or reaching the final coma over a period of a day or so. Signs of brain stem dysfunction—as evidenced by pinpoint pupils, oculomotor dysfunction, nystagmus, facial nerve palsies and dysarthria—are quite common, while signs of meningeal irritation tend to be rare. While signs of cerebellar dysfunction, such as truncal instability and dysmetria of the limbs, may be present, they are often absent.

The diagnosis of cerebellar hemorrhage can usually be confirmed by computerized axial tomography. Lumbar puncture should be avoided since it can cause tonsillar herniation.

Hypertension is the most common cause of cerebellar hemorrhage, which in turn constitutes 10 percent to 15 percent of all intracranial hemorrhages secondary to hypertension. Less common causes are vascular malformations, aneurysms, hemorrhagic diathesis and hemorrhage within a tumor or infarct.[18,19]

Hyperpyrexia

Hyperpyrexia caused by infection or heat stroke may be responsible for a pure cerebellar syndrome. The acute neurological manifestations of profound hyperthermia tend to be those of coma and generalized convulsions, frequently complicated by shock and renal failure. In patients who survive the initial stages of the illness, signs of widespread cerebral dysfunction may be seen: confusion, pseudobulbar palsy and spastic paraparesis. These abnormalities may resolve gradually, leaving the patient with a profound cerebellar syndrome characterized by dysarthria, dysmetria, and ataxia. A study of 125 fatal cases of heat stroke by Malamud and co-workers has shown that the cerebellum seems to be affected to a greater degree than is any other part of the nervous system. Purkinje cells tend to degenerate in all parts of the cerebellum—that is, in the hemispheres and in the vermis.[20]

Familial Ataxias

The familial ataxias are a group of genetically determined disorders that can be loosely classified according to their age of onset. In adults, two distinct disease entities can be recognized: (1) olivopontocerebellar degeneration and (2) cortical cerebellar degeneration. Olivopontocerebellar degeneration usually begins in the fourth or fifth decade of life with symptoms of unsteadiness of gait that progress to severe truncal ataxia, dysmetria of arms and eventually dysarthria. Bowel and bladder sphincters can be involved; in some cases choreiform movements have been described. Sensation, muscle power and reflex activity are usually intact. As the name implies, the disease process involves the medulla, the pons, and the cerebellum. Although olivopontocerebellar degeneration is, in most instances, genetically determined, sporadic cases have also been described. Cortical cerebellar degeneration has its onset relatively late in life. It is a slowly progressive disease characterized by pure cerebellar symptoms and signs. The disease process is confined to the cerebellar cortex. The fact that this disease rarely occurs in more than one member of a family may be due to a dominant mutant gene with incomplete penetrance. In the absence of a family his-

TABLE 2.—*Cerebellar Ataxia in Children*

Acute
Intoxications with drugs or heavy metals
Encephalitis
Posterior fossa tumors
Head injury
Associated with remote neoplasms: such as neuroblastoma
Chronic
Developmental anomalies
Heredofamilial disorders
Friedreich ataxia
Ataxia with muscle atrophy (Roussy-Levy)
Ataxia with myoclonus (Ramsay-Hunt)
Ataxia telangiectasia (Louis-Bar)
Acanthocytosis (Bassen-Kornzweig)
Lipid storage disorders
Miscellaneous
Hartnup disease
Leigh encephalopathy
Intermittent ataxia and pyruvate decarboxylase deficiency

tory, the diagnosis is very difficult to establish. To date, the cause of the familial cerebellar degenerations remains obscure.

DR. DREYFUS: *I have asked Dr. Vijayan to discuss the ataxias most commonly encountered in children.*

Cerebellar Ataxia of Childhood

NAZHIYATH VIJAYAN, MD:* After reviewing the main causes of the cerebellar ataxias that occur in adults, it seems appropriate to discuss some disorders that are encountered predominantly in children. Since time does not permit a complete and detailed discussion of all of the neurological syndromes associated with ataxia, Table 2 provides a list of the most common diseases.

In discussing the acute ataxias of childhood, it is important to keep in mind the entity known as acute cerebellitis (acute cerebellar ataxia),[21] a self-limited disorder characterized by the sudden onset of ataxia, dysmetria and nystagmus, and frequently preceded by a nonspecific upper respiratory infection, headache, vomiting, and, on occasion, drowsiness of brief duration. Fever and nuchal rigidity are usually absent. Examination of the cerebrospinal fluid may show the presence of a few lymphocytes and slight elevation of the protein content; findings on an electroencephalogram may be mildly abnormal in approximately half of the patients examined. A viral cause has been postulated, although the infectious agent has rarely been identified. Several different viruses have been incriminated, including varicella, Echo type 9, coxsackie B, poliomyelitis, measles, mumps and rubella. Of these, varicella has been the one most commonly identified. In the course of viral illnesses with exanthematous manifestations, the rash usually precedes the advent of ataxia; on very rare occasions the sequence of events is reversed. Sometimes signs of brain stem dysfunction—such as cranial nerve palsies, disturbed ocular motility and extensor plantar responses—can be elicited. Acute cerebellitis must be differentiated from a posterior fossa tumor. On occasion this can be accomplished by means of computerized axial tomography. More often, however, the clinical course of the illness points to the correct diagnosis. In most cases of acute cerebellitis, recovery begins in a matter of days and is usually complete within a few weeks. Signs of increased intracranial pressure are rarely detected.

Cerebellar Ataxia Associated With Remote Neoplasms

In adults the association of cerebellar degeneration and the remote, nonmetastatic effects of neoplasia is well recognized. A similar syndrome has been described in children who harbor a neuroblastoma. Characteristically these patients present with ataxia of gait, dysmetria of the extremities, dysarthria, and chaotic eye movements referred to as *opsoclonus,* which resembles nystagmus. Since neuroblastoma cells secrete epinephrine, large concentrations of the breakdown product vanillylmandelic acid (VMA) can be detected in the patient's urine. Neuroblastoma is one of the most common types of solid tumors encountered in children and carries the most favorable prognosis. The distressing neurological symptoms improve or disappear altogether following early diagnosis and removal of the tumor. The underlying physiological mechanisms by which the neoplasm affects cerebellar function remains unknown.[22]

Having discussed two of the important causes of acute ataxia of childhood, let us consider some of the more common chronic forms.

Developmental Anomalies

A number of well-known developmental anomalies of the posterior fossa and the cranio-vertebral junction involve the cerebellum and are responsible for chronic, progressive ataxia. The most common disorders are agenesis of the cerebellum,

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the Dandy-Walker syndrome, and the Arnold-Chiari malformation. *Agenesis of the cerebellum* produces mild ataxia, which lessens with age by virtue of compensatory mechanisms.[23] The *Dandy-Walker syndrome,* a congenital anomaly caused by occlusion of the foramina of the fourth ventricle, leads to dilatation of the fourth ventricle and impairment of cerebellar function. The condition is characterized by a bulging occiput, progressive ataxia, nystagmus, and cranial nerve deficits.[24]

The *Arnold-Chiari malformation,* in which the cerebellum is elongated and the cerebellar tonsils protrude through the foramen magnum into the cervical spinal canal, is commonly associated with such other major anomalies as myelomeningocele, and cerebral and ventricular abnormalities. Although cerebellar ataxia is one of the major symptoms, lower cranial nerve palsies, spinal cord involvement and hydrocephalus are common manifestations. Since the progressive neurological deficit can be retarded by surgical procedures, appropriate diagnostic tests, including air or contrast myelography, should be seriously considered.[23,24]

Hereditary Disorders

A number of hereditary disorders that are characterized chiefly by ataxia are encountered in childhood. The best described are Friedreich ataxia, ataxia telangiectasis, ataxia with myoclonic epilepsy, ataxia associated with abetalipoproteinemia and acanthocytosis, and ataxia associated with a metabolic defect.

Only the most common and well-defined entities will be considered here.

Friedreich ataxia is one of the most common forms of hereditary spinocerebellar ataxias, usually inherited in an autosomal recessive manner. Over half of the cases have their onset before the age of 10 and in most of the cases symptoms develop before the person involved reaches the age of 25. Afflicted members of a family tend to experience the first symptoms of this disease at the same age, but the rate of progression varies considerably from person to person.

The earliest symptoms and signs are related to ataxia of gait. Many children are described as being "slow developers" or clumsy long before ataxia is manifest; however, many afflicted persons give a history of normal growth and development before the onset of ataxia. In many instances, a high-arched deformity of the foot is noted at the time of onset of ataxia. Typically, the ataxia is of the cerebellar type characterized by broadbased gait and incoordination of legs. Subsequently ataxia spreads to the upper extremities and dysarthria develops. As the disease progresses, evidence of posterior column dysfunction—loss of joint position sense, vibratory sense and tactile discrimination—becomes prominent. Impaired posterior column function tends to aggravate the patient's ataxia.

During the early phases of the disease, deep tendon reflexes disappear in the legs; eventually they are lost in the upper extremities as well. Extensor plantar responses tend to develop later. Horizontal nystagmus may be seen in more than half of the patients while dementia is a rare and late complication of the disease.

In addition to neurological manifestations, cardiological manifestations may be observed, such as myocarditis, conduction defects and congestive failure. Because of paraspinous muscle weakness, thoracic kyphoscoliosis is a common complication.

As one might expect, the pathological changes are seen in the dorsal columns, the dorsal and ventral spinocerebellar tracts, and pyramidal tracts of the spinal cord. The dorsal roots are also involved. The underlying metabolic defect that is responsible for the extensive degenerative changes is presently under intense investigation. Abnormalities in pyruvic and oxoglutaric acid metabolism may account for some cases of Friedreich ataxia.[25]

Ataxia telangectasia is a genetic disorder, inherited in an autosomal recessive manner. Progressive ataxia becomes apparent as soon as the child begins to walk. Frequently motor development is delayed, to the point where the average patient does not begin to walk before 16 to 20 months of age. Whereas ataxia begins in the lower extremities, it gradually involves the upper extremities and the bulbar musculature. Speech becomes dysarthric and nystagmus is quite common. As the disease progresses, choreoathetosis may develop. The second most characteristic manifestation of the disease is the appearance of telangectasia, usually around the age of 3. These are first seen in the bulbar conjunctiva, the exposed parts of the ear lobes, flexor creases of the upper and lower extremities and, eventually, over other exposed surfaces of the body. As the patient grows older, telangectasia becomes more extensive. The third feature of the disease is the

patient's susceptibility to chronic sinus, ear and pulmonary infections. The latter may lead to bronchiectasis. Despite the fact that neurological disability progresses fairly rapidly, the patient's mentation usually remains intact. Peripheral neuropathy may be seen as part of the clinical picture.

Immunological abnormalities constitute a common finding. Approximately 75 percent of children afflicted with the disease have either absent or reduced levels of IgA. IgM and IgG are most often normal, but IgG may be reduced in some cases. The low IgA levels are thought to be due to reduced rates of synthesis rather than to increased catabolism. Antibody responses to various antigens tend to be poor. The thymus gland of affected children is either underdeveloped or totally absent and peripheral lymphoid tissues show a pronounced depletion of lymphocytes, leading to lymphopenia.

Treatment of this disease is entirely symptomatic. Appropriate antibiotic agents are of value in treating specific infections of the respiratory tract. The administration of gamma globulin has not proven to be very beneficial.[26]

Ataxia Associated with a Metabolic Defect

Ataxia in children may be caused by a number of genetically determined inborn errors of metabolism. While in most cases ataxia presents in a progressive manner, starting relatively early in life depending upon the defect, it also may be present in intermittent bouts of short duration.

Subacute necrotizing encephalopathy, or Leigh disease, is characterized by ataxia, hypotonia, ophthalmoplegia, dysphagia, disturbed vision or hearing, and evidence of peripheral neuropathy. The necrotic lesions found in the brains of children who succumb to Leigh disease, usually in early childhood, are similar in appearance and distribution to those found in the brains of adult patients afflicted with Wernicke disease. An abnormality in pyruvate oxidation appears to be present in most cases. The faulty enzymatic step in this complex biochemical reaction may differ from patient to patient. The administration of thiamine, an essential cofactor in the metabolism of pyruvate, has been found to be effective treatment in some cases. Pyruvate dehydrogenase deficiency, a disease distinguished by progressive or intermittent bouts of ataxia, may represent a clinical variant of Leigh disease. Some cases are known to be thiamine-responsive.[27,28]

Metabolically determined ataxia is quite commonly associated with some degree of mental retardation. Arginino-succinic aciduria, which is caused by an enzymatic block of the urea cycle enzyme (arginino-succinase); Hartnup disease, thought to be the result of an error in the transport of tryptophan and other neutral amino acids in the renal tubules; and abetalipoproteinemia (Bassen-Kornzweig disease), an abnormality of lipid transport, can all cause ataxia of progressive nature.[29]

Most recently a syndrome of unknown cause characterized by short bouts of ataxia, dysarthria and nystagmus lasting one to two hours and dramatically reduced by the administration of acetazolamide has been described in members of two families (Sauer RN, Dreyfus PM: Familial episodic ataxia [personal observations]).

A metabolic screen on the blood and urine should be obtained in patients whose ataxia is not readily explained by a fixed, a progressive or an expanding lesion within the posterior fossa. The urine should be screened for the presence of amino acids, organic acids and catecholamine breakdown products.

A complete description of the long list of diseases that produce ataxia in children would be too extensive to include here.

DR. DREYFUS: *We have attempted to provide an overview of a common neurological disturbance by discussing its anatomy and physiology, and the most important clinical states in which it occurs. It is hoped that, as the basic pathophysiology of some hitherto obscure disorder is elucidated by means of sophisticated immunological, virological and biochemical techniques, the specific causes of some of these diseases will be discovered, leading to effective methods of therapeutic intervention.*

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Smoking and Lung Cancer

IT TAKES A LONG TIME to produce cancer. It may not take nearly so long to stop it—to prevent it. In the early 1950's, when Sir Richard Dahl and Sir Austin Bradford Hill published their information on the relation of smoking and lung cancer, many British physicians, demonstrating considerable intelligence, stopped smoking. In a period of five to eight years after these reports had been published, the rates in physicians had begun to decline, whereas the rates for all adult males in England were increasing. . . . This is an illness in which the effects of personal prevention take place almost immediately upon someone having taken personal preventative action. You stop smoking. Your rates then are the rates of a smoker at the age at which you had stopped. They do not continue to rise. They actually fall initially, and then gradually approach the rates of the nonsmokers. Here's a personal thing that one can do which has an immediate effect. It doesn't seem to matter how long you've smoked—you can take this action yourself, and it works. People say, "Oh, I've smoked 20 years; I guess it doesn't matter any longer." Only if there has been softening of the brain doesn't it matter any longer.

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